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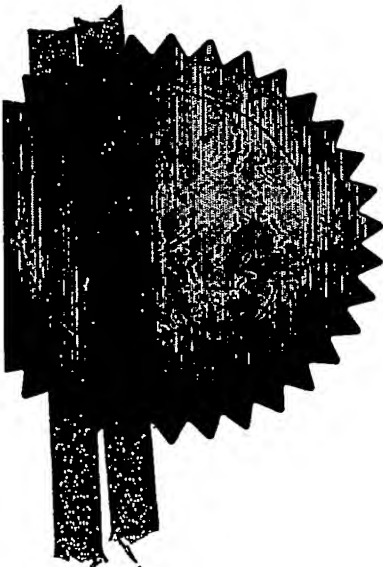
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*Stephen Hordley*

Dated

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2. Patent application number (The Patent office will fill in this part)	0228533.6		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB		
Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its corporation	GB		
4 Title of the invention	CRYSTALLINE FORM		
5 Name of your agent (if you know one)	KAREN CRAWLEY		
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11. I/We request the grant of a patent on the basis of this application

Signature KAREN CRAWLEY 06 December 2002  
AGENT FOR THE APPLICANTS

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### Crystalline Form

The present invention relates to crystalline derivatives of oxopyrrolidine compounds and their use in medicine. More particularly, the invention is concerned

5 with a crystalline form of (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide, pharmaceutical formulations thereof, processes for preparing it, and its use in medicine, particularly use in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.

10

Factor Xa is a member of the trypsin-like serine protease class of enzymes. It is a key enzyme in the coagulation cascade. A one-to-one binding of Factors Xa and Va with calcium ions and phospholipid converts prothrombin into thrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. The insoluble fibrin matrix is required for the stabilisation of the primary hemostatic plug. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Both treatment of an occlusive coronary thrombus by thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) are often accompanied by an acute thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a pre-disposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterised by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure.

25  
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Beyond its direct role in the formation of fibrin rich blood clots, thrombin has been reported to have profound bioregulatory effects on a number of cellular components within the vasculature and blood, (Shuman, M.A., Ann. NY Acad. Sci., 405: 349 (1986)).

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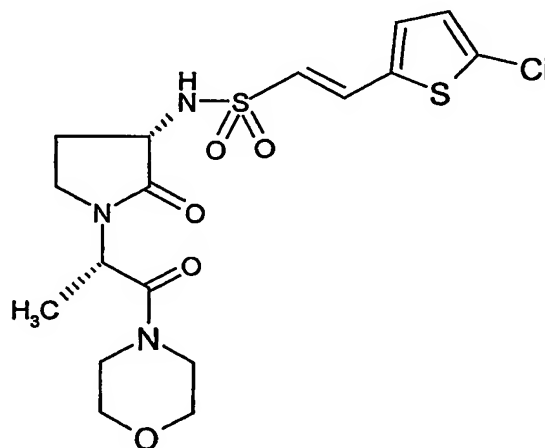
A Factor Xa inhibitor may be useful in the treatment of acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of

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thromboembolic events associated with atrial fibrillation, e.g. stroke. They may also have utility as anti-coagulant agents both in-vivo and ex-vivo, and in oedema and inflammation. Thrombin has been reported to contribute to lung fibroblast proliferation, thus, Factor Xa inhibitors could be useful for the treatment of some

5 pulmonary fibrotic diseases. Factor Xa inhibitors could also be useful in the treatment of tumour metastasis, preventing the fibrin deposition and metastasis caused by the inappropriate activation of Factor Xa by cysteine proteinases produced by certain tumour cells. Thrombin can induce neurite retraction and thus Factor Xa inhibitors may have potential in neurogenerative diseases such as Parkinson's and  
10 Alzheimer's disease. They have also been reported for use in conjunction with thrombolytic agents, thus permitting the use of a lower dose of thrombolytic agent.

(E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide is a FXa inhibitor disclosed in  
15 PCT.GB02.02586 and PCT.GB02.02721 and has the structure shown below:



### Summary of the Invention

20 We have now found that (E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide can be obtained in crystalline form. Thus there is provided in a first aspect of the invention (E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form.

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Further aspects of the invention are:

- A pharmaceutical composition comprising (E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form together with a pharmaceutical carrier  
30 and/or excipient.

- (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form for use in therapy.
- Use of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.
- A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form.

### Description of the Invention

- 15 The crystalline form of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide may be obtained by crystallisation under certain conditions in the form of needle and/or lathe shaped particles, up to 250 microns in length, as described below. There is thus provided in a further aspect of the invention, crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in the form of needle-shaped crystals. There is also provided in a further aspect of the invention, crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in the form of lathe-shaped crystals. There is also provided in a further aspect of the invention, crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in the form of a mixture of needle-shaped and lathe-shaped crystals. Preferably, the crystals are up to 250 microns in length. However, it will be appreciated that alternative crystal habits under certain circumstances can be formed. It is therefore to be understood that all such alternative crystal habits are within the scope of the present invention.

As used herein, the term "needle-shaped" means a needle-like prism. This shape is also known as "acicular". Preferably needle-shaped crystals are up to 250 microns in length.

As used herein, the term "lathe-shaped" means a blade or spatula shaped crystal, in other words a flattened acicular shape. Preferably, lathe-shaped crystals are up to 250 microns in length.

- Crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide has a melting point onset of 163-165°C. There is thus provided in a further aspect of the invention, (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-

oxopyrrolidin-3-yl}ethenesulfonamide in crystalline form having a melting point of 160°C or greater, preferably 163°C or greater, more preferably in the range 163-165°C.

5 A sample of crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide, prepared as described hereinafter, gave the X-ray powder diffraction pattern of Figure 1. The X-ray diffraction pattern is unique to the crystalline form. The crystalline form exhibits a diffraction pattern with a unique set of diffraction peaks which can be expressed in 2  
10 theta angles (°), d-spacings (Å) and/or relative peak intensities.

2 Theta diffraction angles and corresponding d-spacing values account for positions of various peaks in the X-ray diffraction pattern. D-spacing values are calculated with observed 2 theta angles and copper K $\alpha$ 1 wavelength using the Bragg equation.  
15 Slight variations in observed 2 theta angles and d-spacings are expected based on the specific diffractometer employed and the analyst's sample preparation technique. More variation is expected for the relative peak intensities. Identification of the exact crystal form of a compound should be based primarily on observed 2 theta angles or d-spacings with lesser importance place on relative peak intensities. To identify  
20 crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide, the characteristic 2 theta angle peak occurs at 18.39 degrees, or 4.82 Å d-spacing.

Although one skilled in the art can identify crystalline (E)-2-(5-chlorothien-2-yl)-N-  
25 {(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide from the characteristic 2 theta angle peak at 18.39 degrees, in some circumstances it may be desirable to rely upon multiple 2 theta angles or multiple d-spacings for the identification of crystalline (E)-2-(5-chlorothien-2-yl)-N-  
30 {(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide. Crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide can also be identified by the presence of multiple characteristic 2 theta angle peaks including two, three, four, or all five of the 2 theta angles which are reasonably characteristic of this particular crystalline form. These peaks occur at the following positions,  
35 expressed in 2 theta angles: 9.21, 13.79, 16.11, 18.11, 18.39 degrees. In one embodiment at least one of the foregoing 2 theta angles are employed to identify crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide.

40 Some margin of error is present in each of the 2 theta angle assignments and d-spacings reported above. The error in determining d-spacings decreases with increasing diffraction scan angle or decreasing d-spacing. The margin of error in the foregoing 2 theta angles is approximately  $\pm 0.05$  degrees for each of the foregoing

peak assignments. The margin of error in d-spacing values is approximately  $\pm 0.05$  Angstroms.

Since some margin of error is possible in the assignment of 2 theta angles and d-spacings, the preferred method of comparing X-ray powder diffraction patterns in order to identify a particular crystalline form is to overlay the X-ray powder diffraction pattern of the unknown form over the X-ray powder diffraction pattern of a known form. For example, one skilled in the art can overlay an X-ray powder diffraction pattern of an unidentified form of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide, obtained using the methods described herein, over Figure 1 and readily determine whether the X-ray diffraction pattern of the unidentified form is substantially the same as the X-ray powder diffraction pattern of crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide. If the X-ray powder diffraction pattern is substantially the same as Figure 1, the previously unknown form can be readily and accurately identified as crystalline (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide.

Although 2 theta angles or d-spacings are the primary method of identifying a particular crystalline form, it may be desirable to also compare relative peak intensities. As noted above, relative peak intensities may vary depending upon the specific diffractometer employed and the analyst's sample preparation technique. The peak intensities are reported as intensities relative to the peak intensity of the strongest peak. The intensity units on the X-ray diffraction plot are counts/sec. The absolute counts = counts/time x count time = counts/sec x 10 sec.

In a further preferred aspect the invention provides (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form substantially free of amorphous form (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide. By "substantially free" is meant containing less than 20% of the amorphous form, preferably less than 10% of the amorphous form, more preferably less than 5% of the amorphous form, even more preferably less than 2% of the amorphous form, most preferably less than 1% of the amorphous form.

(E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide may be prepared in crystalline form by crystallisation from aqueous solution. In general, (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide is dissolved in an organic solvent, for example a ketone such as acetone, preferably at elevated temperature e.g. 50-60°C, and then water is added as a counter-solvent. Crystallisation is carried out by reducing the temperature of the solution, preferably to



room temperature. Preferably, the crystals of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide are isolated by filtration.

- 5 The methods for the preparation of crystalline material described herein constitute a further aspect of the present invention.

(E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide is a Factor Xa inhibitor and as such is useful in  
10 the treatment of clinical conditions susceptible to amelioration by administration of a Factor Xa inhibitor. Such conditions include acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks,  
15 pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke; in oedema and PAF mediated inflammatory diseases such as adult respiratory shock syndrome, septic shock and reperfusion damage; the treatment of pulmonary fibrosis; the treatment of tumour  
20 metastasis; neurogenerative disease such as Parkinson's and Alzheimer's diseases; viral infection; Kasabach Merritt Syndrome; Haemolytic uremic syndrome; arthritis; osteoporosis; as anti-coagulants for extracorporeal blood in for example, dialysis, blood filtration, bypass, and blood product storage; and in the coating of invasive devices such as prostheses, artificial valves and catheters in reducing the risk of  
25 thrombus formation.

Accordingly, one aspect of the present invention provides (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form for use in medical therapy, particularly for  
30 use in the amelioration of a clinical condition in a mammal, including a human, for which a Factor Xa inhibitor is indicated.

In another aspect, the invention provides a method for the treatment and/or prophylaxis of a mammal, including a human, suffering from a condition susceptible  
35 to amelioration by a Factor Xa inhibitor which method comprises administering to the subject an effective amount of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form.

In another aspect, the present invention provides the use of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form, for the manufacture of a medicament for the  
40 treatment and/or prophylaxis of a condition susceptible to amelioration by a Factor Xa inhibitor.

Preferably, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from treatment of acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel

5 closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

10

More preferably, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from coronary thrombosis (for example myocardial infarction and unstable angina), pulmonary embolism, deep vein thrombosis and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke;

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It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

20

While it is possible that, for use in therapy, (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide in crystalline form may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

25

In a further aspect, the invention provides a pharmaceutical composition comprising (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide in crystalline form in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

30

Accordingly, the present invention further provides a pharmaceutical formulation comprising (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide in crystalline form, in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or

35

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide in crystalline form in association with a pharmaceutically acceptable carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

40

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide in crystalline form, together with a pharmaceutically acceptable carrier and/or excipient.

(E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide in crystalline form may be formulated for oral, buccal, parenteral, topical, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions or they may be presented as a dry product for constitution with water or other suitable vehicles before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound using a pharmaceutically acceptable carrier and/or excipients, e.g. hydroxypropyl methylcellulose.

For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner.

The compounds according to the present invention may be formulated for parenteral administration by injection, e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing

agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

5 The compounds according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator.

10 Powders for external application may be formed with the aid of any suitable powder base, for example, lactose, talc or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

15 The compounds according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

20 In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

25 A proposed dose of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably to 1mg to 500mg of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The dosage will also depend on the route of administration.

30 The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

40 (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form together with a further therapeutic agent.

When (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form is used in combination with a second therapeutic agent active against the same disease state

5 the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant  
10 physician or veterinarian. (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form may be used in combination with other antithrombotic drugs such as thrombin inhibitors, thromboxane receptor antagonists, prostacyclin mimetics, phosphodiesterase inhibitors, fibrinogen antagonists, thrombolytic drugs such as  
15 tissue plasminogen activator and streptokinase, non-steroidal anti-inflammatory drugs such as aspirin, and the like.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations  
20 comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

25 When administration is sequential, either the Factor Xa inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

30 When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such  
35 compounds in the art.

The present invention will now be further illustrated by the accompanying examples which should not be construed as limiting the scope of the invention in any way.

40 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

### Examples

#### Intermediate 1

##### 5 *tert*-Butyl N-[(benzyloxy)carbonyl]-L-methionyl-L-alaninate

10 Z-Protected L-methionine (10g) was dissolved in DMF (200ml) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.13g) was added followed by HOBt (5.72g) and triethylamine (19.7ml). The mixture was stirred for 1h then L-alanine *tert*-butyl ester (7.7g) was added and stirring continued for 18h. The mixture was concentrated under reduced pressure and partitioned between diethyl ether and water. The separated organic phase was washed with hydrochloric acid (1M), saturated sodium bicarbonate solution and brine, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (11.9g) as an orange oil which crystallised on standing.

15 Mass spectrum: Found:  $MH^+$  411

#### Intermediate 2

##### *tert*-Butyl (2S)-2-((3S)-3-[(benzyloxy)carbonylamino]-2-oxopyrrolidin-1-yl)propanoate

20 A solution of Intermediate 1 (11.9g) in acetone (75ml) was treated with methyl iodide (18ml) and stirred at room temperature for 72h. The reaction mixture was then concentrated under reduced pressure to give an orange solid which was dissolved in acetonitrile (200ml). Dowex ( $OH^-$  form) resin (19.42g) was added and the mixture stirred for 18h at room temperature. The mixture was filtered and the resin washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford a yellow oil which was purified by Biotage<sup>TM</sup> chromatography (eluting with cyclohexane:ethyl acetate 3:2) to give the title compound (2.92g) as a colourless oil. Mass spectrum: Found:  $MH^+$  363

#### 30 Intermediate 3

##### (2S)-2-((3S)-3-[(Benzyloxy)carbonylamino]-2-oxopyrrolidin-1-yl) propanoic acid

Intermediate 2 (0.5g) was dissolved in DCM (7ml), and trifluoroacetic acid (4.7ml) was added. The mixture was stirred at room temperature for 1.5h and then concentrated under reduced pressure to give the title compound (0.423g) as a colourless oil which after azeotropeing with toluene, crystallised.

35 Mass spectrum: Found:  $MH^+$  307

#### Intermediate 4

##### 40 Benzyl (3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-ylcarbamate

Intermediate 3 (84.5g) was dissolved in DMF (2l) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161g) was added, followed by N,N-diisopropylethylamine (92ml) and morpholine (46ml). The mixture was stirred under

nitrogen for 2.5h, and saturated aqueous ammonium chloride was added. The mixture was stirred for 15min then partitioned between water and ethyl acetate. The separated organic phase was washed with lithium chloride (10% by weight), followed by saturated sodium bicarbonate and brine. The organic layer was dried (over sodium sulphate) and concentrated under reduced pressure to give the title compound (65g) as a yellow solid.

Mass spectrum: Found:  $MH^+$  376

#### Intermediate 5

##### (3S)-3-Amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one

A mixture of Intermediate 4 (20g), 10 % palladium on carbon (2g) and ethanol (1.3l) was stirred under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through Celite<sup>TM</sup> and the filtrate was concentrated under reduced pressure to give the title compound (12.3g) as a pale white oil.

<sup>1</sup>H NMR (D<sub>4</sub>MeOH):  $\delta$ 5.05(1H, dd), 3.59(9H, m), 3.37(2H, m), 2.42(1H, m), 1.75(1H, m), 1.30(3H, d) ppm.

#### Example 1

##### (E)-2-(5-chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide

To a solution of Intermediate 5 (14.9g) in anhydrous acetonitrile (750ml) were added (E)-2-(5-chlorothien-2-yl)ethanesulfonyl chloride (16.5g) in acetonitrile (250ml) and pyridine (11ml), and the mixture was stirred at room temperature for 72h. Saturated ammonium chloride solution was added and the resultant mixture stirred at room temperature for 30min. The mixture was concentrated under reduced pressure and the residue partitioned between chloroform and a 1:1 mixture of hydrochloric acid (2M) and water. The organic layer was washed with a 1:1 mixture of saturated sodium bicarbonate and water, and brine. The organic layer was isolated, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (19.3g) as a white solid (amorphous form).

Mass spectrum: Found:  $MH^+$  448

H.p.l.c. Rt 2.99min

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ 7.48(1H, d), 7.08(1H, d), 6.90(1H, d), 6.55(1H, d), 5.12(1H, br.d), 5.06(1H, q), 3.96(1H, m), 3.70-3.48(9H, m), 3.35(1H, m), 2.62(1H, m), 2.05(1H, m), 1.34(3H, d) ppm.

#### Crystallisation of Example 1

Example 1 (33.3g) was dissolved in acetone (350ml) at 55°C, whilst stirring under nitrogen. Water (780ml) was added dropwise and in portions over 3.5h, during which the solution began to appear cloudy. The heat was removed and the solution left to reach room temperature over 2h. The mixture was left for a further 18h at room temperature in the absence of light. The resultant suspension was filtered, washed

with cold water (200ml), and then dried under vacuum at 30°C over 24h, to give the title compound as a white crystalline solid.

- 5 The crystalline material obtained was used as a seed to initiate crystallisation in a repeat crystallisation process (as described above) in which the seed was added after removing the heat to give the title compound (29.2g) as a white crystalline solid.

Melting point (by DSC): melting onset 163 to 165 °C

- 10 The crystalline solid exists predominately as needle-shaped and lathe-shaped particles, up to 250 microns in length, which form loose agglomerates.

- 15 The X-ray powder diffraction pattern of the crystalline compound as shown in Figure 1 was obtained using the settings shown in Table 1. Table 2 lists characteristic peak data.

Table 1. XRPD instrument details and measurement conditions

Manufacturer	Philips Analytical X-Ray B.V. The Netherlands
Diffractometer type	PW3040
Serial	DY667
Tube Anode	Cu
LabdaAlpha 1	1.54056
LabdaAlpha 2	1.54439
Ratio Alpha21	0.50000
Divergence slit	Prog. Div. Slit
Receiving slit	Prog. Rec. Slit
Monochromator used	YES
Generator voltage	40
Tube current	50
File data & time	31 July 2002
Data angle range (° 2θ)	2.0000 – 45.0000
Scan step size (° 2θ)	0.02000
Scan type	Continuous
Scan step time	1. 00 seconds



Table 2. XRPD peak data for crystalline Example 1; characterized by an X-ray powder diffraction pattern that contains but is not limited to the peaks in Table 2.

Angle (°2θ)	d K-alpha1 (Å)	Relative Intensity (%)
9.21	9.60	17.5
10.82	8.17	3.2
12.41	7.13	3.3
13.79	6.42	11.5
14.38	6.16	3.2
16.11	5.50	13.2
16.64	5.32	5.9
16.80	5.27	6.7
18.11	4.89	16.8
18.39	4.82	100.0
20.25	4.38	3.7
20.62	4.30	3.1
21.14	4.20	4.0
22.37	3.97	9.6

5

The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of product, process or use claims and may include, by way of example and without limitation, the claims that follow.

10

CLAIMS

1. (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form.
- 5 2. The crystalline form as claimed in claim 1 in the form of needle-shaped crystals.
3. The crystalline form as claimed in claim 1 in the form of lathe-shaped crystals.
- 10 4. The crystalline form as claimed in claim 1 in the form of a mixture of needle-shaped and lathe-shaped crystals.
5. The crystalline form as claimed in any one of claims 1-4 wherein the melting point is greater than 160°C.
- 15 6. The crystalline form as claimed in claim 1 having an X-ray powder diffraction pattern expressed in terms of 2 theta angles and obtained with a diffractometer, wherein said X-ray powder diffraction pattern comprises 2 theta angles at one or more positions selected from the group consisting of  $9.21 \pm 0.05$ ,  $13.79 \pm 0.05$ ,  $16.11 \pm 0.05$ ,  $18.11 \pm 0.05$ , and  $18.39 \pm 0.05$  degrees.
- 20 7. The crystalline form as claimed in claim 1 for which the X-ray diffraction data are as shown in Table 2.
- 25 8. The crystalline form as claimed in any one of claims 1-7 substantially free from amorphous material.
9. A method for the preparation of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form as claimed in any one of claims 1 to 8, which method comprises crystallisation of (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide from aqueous solution.
- 30 10. (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form as claimed in any of claims 1 to 8 for use in therapy.
- 35 11. A pharmaceutical composition comprising (E)-2-(5-chlorothien-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form as claimed in any of claims 1 to 8 together with a pharmaceutical carrier and/or excipient.
- 40

12. Use of (E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form as claimed in any of claims 1 to 7 for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

5

13. A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of (E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form as claimed in any of claims 1 to 8.

10

**ABSTRACT**

(E)-2-(5-chlorothiophen-2-yl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide in crystalline form, pharmaceutical formulations

5 thereof, processes for preparing it, and its use in medicine, particularly use in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.

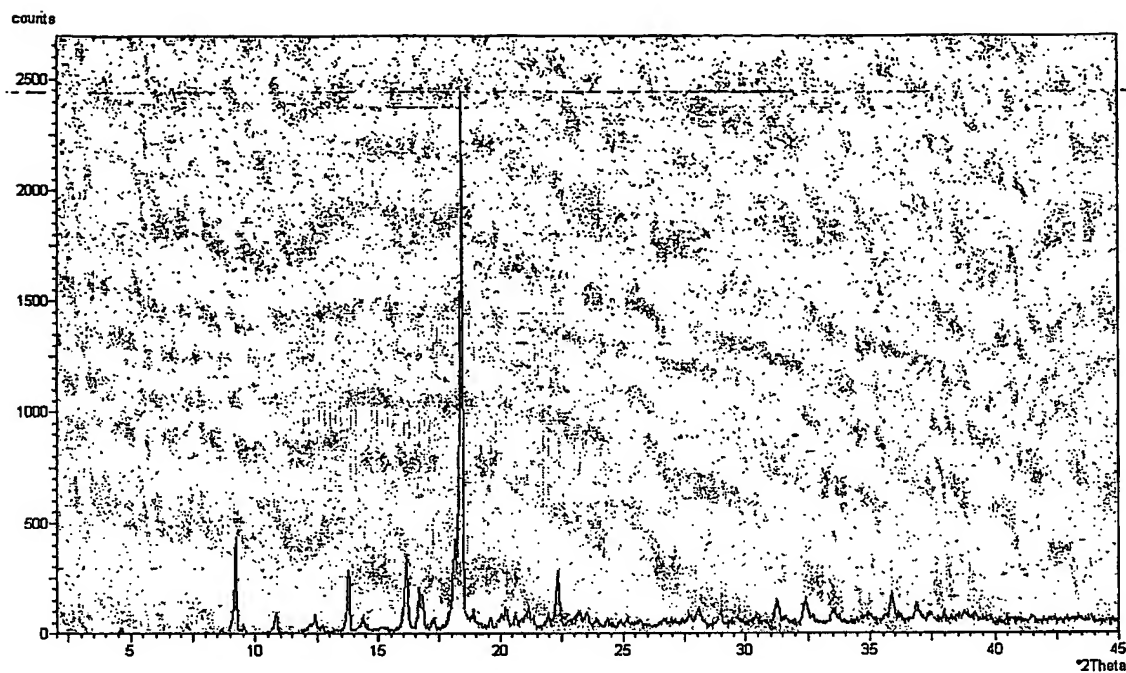


Figure 1. X-Ray Powder Diffractogram of crystalline Example 1.

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